

Remarks

Applicants thank the Examiner for withdrawing the finality of the previous Office Action pursuant to 37 CFR § 114. Applicants also thank the Examiner for considering the amendment filed December 11, 2008, and Applicants' responses filed April 4, 2008, and August 1, 2008. Applicants further thank the Examiner for withdrawal of the prior rejection of record of claims 13 and 38 and claims 17 and 42 under U.S.C. § 103(a).

I. Status of the Claims

Reconsideration of this application is respectfully requested.

Upon the entry of the foregoing amendment, claims 2-6, 9, 11, 13-15, 20-22, 25, 27-31, 34, 36, 38-39, 45-47, 50, 74-77, and 79-87 are pending in the application, with claims 85, 86, and 87 being the independent claims. Claim 74 is herein amended to address the Examiner's arguments. Applicants have made additional clarifying amendments to claims 2-6, 11, 13, 15-16, 20, 23-25, 27-31, 36, 38-40, 45, 48-50, and 74-84 to address some informalities that they noticed, but that were not objected to by the Examiner. Those clarifying amendments were made, nonetheless, to improve the clarity of the claims. Claims 7-8, 16, 23-24, 32-33, 40-41, 48-49, and 78 are currently withdrawn. Original independent claims 1, 26, and 73 have been cancelled and new independent claims 85, 86, and 87 have been added to address certain formality issues as well as to rearrange the claims in order to present them in a clearer form. These changes are believed to introduce no new matter, and their entry is respectfully requested.

II. Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claim 74 under 35 U.S.C. § 112, second paragraph as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter.

The Examiner states that "[c]laim 74 recites the limitation 'system' in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim. Base claim 73 recites 'kit'". Office Action at page 3. Applicants respectfully rebut this rejection.

However, solely to facilitate prosecution of the application, but not in acquiescence with the Examiner's rejection, Applicants have now amended claim 74 to read "kit" in place of "system". Accordingly, Applicants respectfully request that the rejection be withdrawn.

III. Rejections Under 35 U.S.C. § 103

Claims 1-6, 9, 11, 20-22, 25-31, 34, 36, 45-47, 50, 79 and 81 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 92/07952 A1 (hereinafter, "Rothbard") in view of US 2003/0191286 A1 (hereinafter, "Hildebrand"). Applicants have cancelled independent claims 1 and 26, rendering the rejections moot. Insofar as the rejections apply to new independent claims 85 and 86, Applicants respectfully traverse these rejections.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 745 F.2d 1468, 1471-73 (Fed. Cir. 1984). As set forth in *Graham v. John Deere Co. of Kansas City*,

[u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined.

383 U.S. 1, 17 (1966).

In addition, the Examiner must show reasons, explicit or otherwise, that would compel one of ordinary skill in the art to combine the references in order to make and use the

claimed invention. To determine whether there is "an apparent reason to combine" the known elements in the way an application claims,

it will be necessary. . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art. . . . To facilitate review, this analysis should be made explicit.

Id. at 14; *see also* Memorandum from the United States Patent and Trademark Office, "Supreme Court decision on *KSR Int'l. Co. v. Teleflex, Inc.*," (May 3, 2007) ("The Court did not totally reject the use of 'teaching, suggestion, motivation' as a factor in the obviousness analysis. . . . [I]n formulating a rejection . . . based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.").

Applicants assert that the cited references fail to teach or suggest the claimed methods and provide no apparent reason to combine the references cited by the Examiner to arrive at the claimed invention. Applicants further assert that a person of ordinary skill in the art would have no reasonable expectation of success in making the claimed invention.

The currently pending claims are directed to a method for identifying an MHC-binding peptide or measuring relative affinity for an MHC binding peptide. The method comprises:

(a) incubating under a liquid phase condition a ternary complex comprising at least one HLA-A2 monomer having bound thereto a homogeneous template MHC-binding peptide and beta-2 microglobulin, and wherein said monomer is produced in an expression system selected from the group consisting of a prokaryotic system, a yeast system, a plant system, and an insect system;

- (b) an *excess* amount of a first competitor peptide,
- (c) a tracer MHC-binding peptide tagged with a detectable label, wherein the template peptide has *lower affinity* than the tracer peptide for the monomer, and
- (d) detection of the bound peptide by determining a *difference* in signal produced by the detectable label in the total sample as compared with signal produced solely by monomer obtained from the sample after the incubation, wherein the difference indicates affinity of the first competitor peptide for the monomer.

The Examiner states with respect to Rothbard that "[a]lthough the art reference does not explicitly teach 'wherein the template peptide has lower or intermediate affinity as compared with the tracer peptide for the monomer', the art reference teaches that there is peptide exchange and measurement of radioactively labeled tracer peptide and also teaches that the preloaded peptide is preferably chosen to be comparatively readily released by the MHC molecule. Therefore, the claimed method appears to be similar to the method of the prior art absent a showing of unobvious differences". Office Action at page 4. Applicants respectfully disagree with the Examiner's statement.

Rothbard does not disclose, suggest, or otherwise contemplate the method of the claimed invention. Rothbard teaches a first method in which MHC glycoproteins preloaded with a heterogeneous mixture of endogenous peptides is incubated with a detectable agonist (tracer peptide) in the presence of a competitor candidate moiety "under conditions where the agonist is known to form a complex with the MHC glycoprotein". The resulting complex is separated from the reaction mixture, and the effect of the candidate moiety on the agonist included in the complex is measured. *See* Rothbard at page 4, lines 1-9, page 5, lines 12-24, and page 10, lines 8-19.

However, Rothbard does not indicate what is meant by "under conditions where the agonist is known to form a complex with the MHC glycoprotein". Applicants assert that an agonist may displace an endogenous peptide to form a complex with the MHC monomer in one of two ways: (a) when the affinity for the monomer of the agonist is higher than those of the endogenous peptides and (b) when the agonist is present in a molar excess so as to displace the endogenous peptides, irrespective of their relative binding affinities to the MHC monomer. Applicants assert that Rothbard does not differentiate between these two cases. In fact, Rothbard states that "the agonists will be at a concentration of about *0.1-50 times* the concentration of the MHC glycoprotein". See Rothbard at page 9, lines 3-5. Applicants assert that in view of this large concentration range of the agonist peptide, it would not have been obvious to a person of skill in the art which method to apply to create "conditions where the agonist is known to form a complex with the MHC glycoprotein".

In contrast, the claims of the instant invention clearly mention that the recombinant HLA-A2 monomer or modified HLA-A2 monomer is formed preloaded with *homogeneous* template peptide. Furthermore, the template and tracer peptides are chosen such that the template peptide has "lower affinity as compared with the tracer peptide for the monomer" and "wherein the tracer peptide displaces at least 90% of the template peptide in a parallel competition assay conducted in the absence of the first competitor peptide".

Rothbard discloses a second method involving the following steps:

(a) overnight incubation of purified MHC glycoproteins, containing bound heterogeneous endogenous peptides, with a homogeneous preloading peptide agonist for a time sufficient to replace the endogenous peptides,

(b) *dilution* of the preloaded MHC complexes to dissociate the homogeneous peptide agonist from the MHC complex, and

(c) incubation of the MHC protein with the incoming agonist or candidate moiety, and

(d) detecting the amount of agonist bound in the complex as a function of the concentration of candidate moiety in the reaction mixture.

See Rothbard at page 4, lines 19-35, page 6, lines 4-18, page 13, line 20 through page 14, line 8, and page 21, lines 13-18.

Thus, Rothbard teaches in the second method that the MHC monomer is first stripped off the template peptide by dilution and the "empty pocket" of the MHC monomer is then occupied by the incoming tracer or competitor peptide. *See* Rothbard at page 13, lines 30-34, and page 14, lines 20-21.

In contrast, the present invention claims a method in which the recombinant HLA-A2 monomer or modified HLA-A2 monomer is formed *preloaded* with homogeneous template peptide. The homogeneous template peptide is selected such that it has "lower affinity as compared with the tracer peptide for the monomer".

The Examiner points out that Rothbard teaches "the homogeneous, preloaded peptide is preferably chosen to be comparatively readily released by the MHC glycoprotein". Office Action at page 3. However, Applicants contend that this statement is made in the context of the peptide being easy to dislodge from the MHC monomer upon dilution of the monomer. *See* Rothbard at page 4, lines 31-34. No mention is made in Rothbard regarding the comparison of the binding affinity of the homogeneous preloaded template peptide for the MHC monomer *vis-a-vis* that of the tracer peptide.

In view of the above arguments, Applicants maintain that Rothbard does not teach a method involving a template peptide bound to an MHC monomer "wherein the template peptide has lower affinity as compared with the tracer peptide for the monomer".

Further, the instant invention claims a concentration of competitor peptide which is *about or more* than 100-fold molar excess compared to the tracer peptide. However, Rothbard discloses that the amount of the competitor ("candidate") peptide is *not more* than about 100-fold from the amount of the tracer peptide ("agonist") present in the medium. *See* Rothbard at page 9, lines 18-20.

In addition, the instant invention claims a method of detection of the bound peptide by determining a *difference* in signal produced by the detectable label in the total sample as compared with signal produced solely by monomer obtained from the sample after the incubation, wherein the difference indicates affinity of the first competitor peptide for the monomer. However, Rothbard teaches determination of the labeled tracer peptide bound to the MHC molecule as a *function* of the concentration of the competitor peptide in the reaction mixture. *See* Rothbard at page 5, lines 23-24. Thus, Rothbard does not disclose or suggest determining a *difference* in signal in the total sample as compared with the signal produced solely by the isolated monomer in the presence of absence of the competitor peptide as claimed in the instant application.

The Examiner further contends that while "WO 92/07952 A1 does not teach that the MHC molecule is HLA-A2", "[i]t would have been prima facie obvious to one of ordinary skill in the art to have used the soluble HLA-A2 monomers disclosed by US 2003/0191286 A1 as the MHC molecule in the method taught by WO 92/07952 A1". Office Action at pages 3 and 4.

Applicants assert that while Hildebrand (US 2003/0191286 A1) discloses the use of soluble HLA-A2 monomers, the deficiencies of Rothbard, as discussed above, are not overcome by the disclosure of Hildebrand. The Examiner states that "US 2003/0191286 A1 discloses making MHC class I molecules, including HLA-A2, with or without endogenous peptides loaded therein, and further discloses representative HLA-A2 binding peptides of nine or ten amino acid residues in length". Office Action at page 4. However, as noted above, Rothbard fails to disclose the method of the claimed invention. The Examiner does not argue that Hildebrand discloses the elements of the claimed method that are missing in Rothbard. Therefore, Applicants maintain that Hildebrand does not combine with Rothbard to disclose the method of the claimed invention.

Therefore, in view of the aforementioned arguments, Applicants respectfully submit that the Examiner failed to establish a *prima facie* case of obviousness and that the rejections be withdrawn.

The Examiner states "[w]ith regard to the limitation recited in instant claims 4 and 29 'wherein said liquid phase condition includes incubating the sample for about 2 to 20 hours,' the art reference teaches incubating 2 days or 48 hours, and so meets the claim limitation". Office Action at page 5.

The Examiner further points out that "[w]ith regard to the limitation recited in instant claims 5 and 30 'wherein said liquid phase condition further includes incubating the sample at about 21 degrees C,' the art reference teaches incubating at room temperature of 37 degrees C, and so meets the claim limitation". *Id.*

The Examiner also states that "[c]laims 1-6, 9, 11, 20-22 and 25 are included in this rejection because the art method of measuring affinity of a peptide of interest is also identifying said peptide for binding to MHC". *Id.*

The Examiner further states that "[w]ith regard to the recited limitation in instant claims 3 and 28, the said limitation is not a test step. Although the art reference does not explicitly teach 'wherein the tracer peptide displaces at least 90% of the template peptide in a parallel competition assay conducted in the absence of the first competitor peptide,' the art reference teaches that there is peptide exchange and measurement of radioactively labeled tracer peptide and also teaches that the preloaded peptide is preferably chosen to be comparatively readily released by the MHC molecule. Therefore, the claimed method appears to be similar to the method of the prior art absent a showing of unobvious differences". *Id.* Applicants respectfully traverse these rejections.

As discussed *supra*, it would not have been possible for a person of skill in the art to reconstitute the present invention from the teachings of Rothbard, either alone or in view of Hildebrand. Thus, Applicants assert that a person of skill in the art would not have looked to combine disparate portions of Rothbard to reconstruct the instant invention. Nor does the Examiner provide any logical reason or explanation as to what would motivate a skilled artisan, at the time of the invention, to do so.

Thus, Applicants submit that the Examiner's reasoning to reject the above claims under 35 U.S.C. § 103(a) over Rothbard constitutes improper hindsight analysis.

Numerous courts have warned against the use of hindsight analysis in an obviousness analysis:

[D]ecomposing an invention into its constituent elements, finding each element in the prior art, and then claiming that it is easy to reassemble these elements into the invention, is a forbidden ex post analysis.

In re Mahurkar Patent Litigation, 831 F. Supp. 1354, 1359, 28 U.S.P.Q.2D (BNA) 1801, 1805 (N.D. Ill. 1993)

[I]t is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious.

In re Fritch, 972 F.2d. 1260, 1265, 23 U.S.P.Q.2D (BNA) 1780, 1783 (Fed. Cir. 1992).

Applicants maintain that a person of ordinary skill in the art would not have reconstructed the present invention from the disclosure of Rothbard, either alone or in view of Hildebrand.

In view of the foregoing, Applicants submit that the Examiner fails to establish a *prima facie* case of obviousness. Thus, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be reconsidered and withdrawn.

Claims 13, 14, 38, 73-77, 80, 82, 83 and 84 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 92/07952 A1 in view of US 2003/0191286 A1 ("the combined references") as applied to claims 1-6, 9, 11, 20-22, 25-31, 34, 36, 45-47, 50, 79 and 81 above, and further in view of Mitchell *et al.* (Cancer Research 2000, 60: 6448-6456) ("Mitchell"), US 2004/0214995 A1 and US 2002/0106708 A1. Applicants have cancelled claim 73, rendering the rejection moot. Insofar as the rejection applies to new independent claim 87, Applicants respectfully traverse the rejection.

The Examiner states "[t]he combined references do not teach wherein the monomer is HLA-A2/MART-1₂₆₋₃₅ (claims 13 and 38), nor wherein the tracer peptide is HBc 18-27 (claim 14), nor wherein the HLA-A2 monomer is that produced in *E. coli* (claims 80, 82 and 84), nor wherein the ternary complex comprising the HLA-A2 monomer with template MHC-binding peptide and the tracer peptide tagged with a detectable label are comprised in a kit for identifying an MHC binding peptide for the HLA-A2 monomer (claims 73-77, 83 and 84), nor wherein the kit further comprises an instruction for using the kit (claim 74)". Office Action at page 8.

The Examiner further states that "Mitchell *et al* teaches use of the HBc 18-27 peptide labeled with a detectable label and competing unlabeled putative epitope peptides for binding to HLA-A2." *Id.*

The Examiner also states that "US 2004/0214995 A1 discloses the low affinity peptide MART-1₂₆₋₃₅ that binds to HLA-A2 ([0224]), and also discloses the production of proteins in *E. coli*. US 2002/0106708 A1 discloses placing the components of assays into kits (see entire reference)". *Id.*

The Examiner contends that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the MART-1₂₆₋₃₅ peptide as the template MHC binding peptide bound to HLA-A2 in the method taught by the combined references, to have used an HLA-A2 monomer that was produced in *E. coli*, and to have placed the components of the assay (i.e., the monomer with template binding peptide bound thereto and a tracer MHC-binding peptide tagged with a detectable label) in a kit, including with instructions for use". *Id.* at page 9. Applicants respectfully disagree with the Examiner's contentions.

As discussed above, it would not have been possible for a person of skill in the art to reconstitute the present invention from the teachings of Rothbard, either alone or in view of Hildebrand. Thus, Applicants maintain that there would have been no apparent reason for one of ordinary skill in the art to combine Rothbard with any of the other cited references. Applicants assert that a person of skill in the art would not have looked to combine disparate portions of Rothbard with any of the other cited references to construct the instant invention. Nor does the Examiner provide any logical reason or explanation as to what would motivate a skilled artisan, at the time of the invention, to do so.

Applicants submit that the Examiner's reasoning to reject claims 13, 14, 38, 73-77, 80, 82, 83 and 84 under 35 U.S.C. § 103(a) over Rothbard in view of Hildebrand and further in view of Mitchell, US 2004/0214995 A1 and US 2002/0106708 A1 constitutes improper hindsight analysis. As explained above, numerous courts have warned against the use of hindsight analysis in an obviousness analysis.

In view of the foregoing, Applicants submit that the Examiner failed to establish a *prima facie* case of obviousness. Thus, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be reconsidered and withdrawn.

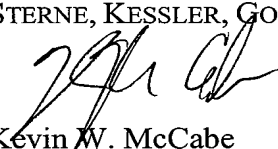
Conclusion

All of the stated grounds of objections and rejections have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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